

Amendments to the Drawings

The attached sheet of drawings includes changes to Figure 9. This sheet, which includes Figure 9, replaces the original Fig.9. In new Figure 9, explanatory terms have been added and numerical identifiers have been corrected. The attached sheets of drawing also include an additional Figure 10.

Attachment: Replacement Sheets- Figure 9
- Additional Figure 10
Annotated sheets showing changes- Figure 9

Remarks/Arguments

The Applicant notes that in the Office Action Summary enclosed with the Office Action dated January 21, 2004, claims 1, 2, 4, 5 and 7 are rejected and claims 3, 6 and 8-10 are withdrawn. However, in the body of the Office Action, the Examiner refers to claims 1, 2, 3, 5 and 6. Therefore, please note that Applicant has provided comments with respect to the patentability of new claims 11 to 18 which are based on old claims 1, 2, 4, 5 and 7.

The Examiner has rejected old claims 1, 2, 4, 5 and 7 on a number of grounds which will be addressed here below. The Applicant respectfully submits that the nature of the invention resides in the appreciation that one may combined C3 or Y27632 with matrix forming elements being capable once intermingled of forming a flowable carrier component, and which elements further being capable of forming a therapeutically acceptable in vivo fibrin matrix and not in the identity of C3 itself.

By the present amendment, the Applicant thus proposes to replace pending claim 1, 2, 4, 5 and 7 with new claims 11 to 18. More particularly, old independent claim 1 has been replaced with new independent claim 11 and old independent claim 5 has been replaced with new independent claim 14. Old dependent claim 2 has been replaced with new dependent claim 12. Claims 13 and 15 to 18 are new.

As mentioned above, old claim 1 has been replaced with new claim 11. In new claim 11, the expression "one or two separate component" now refers to "a first matrix forming element" and "a second matrix forming element". Support for this expression may be found, for example, at page 45, line 25 of the description. The expression "a therapeutically acceptable matrix" now refers to "a therapeutically acceptable in vivo fibrin matrix". Support for this expression may be found, for example, in old claim 4. The expression "and whereby at least one of said first and second container means further comprises a therapeutically active agent selected from the group consisting of C3 and Y-27632" was also added in new claim 11. Support for this expression may be

found, for example, at page 32, lines 2 and 3, in the “Examples” section and more particularly at page 35, line 5 to 18, and at page 17, line 18 of the description.

As mentioned above, old claim 5 has been replaced with new claim 14. More particularly, in new claim 14, the expression “at least one supplement selected from the group consisting of therapeutically active agents for facilitating axon growth” was replaced with the expression “a therapeutically active agent selected from the group consisting of C3 and Y-27632 for facilitating axon growth”. The expression “a flowable carrier component capable of forming a therapeutically acceptable matrix in vivo at a nerve lesion site” was replaced with the expression “a first matrix forming element capable of forming a flowable carrier component once intermingled with a second matrix forming element, and said first and second matrix forming elements further being capable of forming a therapeutically acceptable in vivo fibrin matrix at a nerve lesion site”. Finally the expression “wherein said supplement is releasable from said matrix into the adjacent external environment” was replaced with the expression “wherein said therapeutically active agent is releasable from said in vivo fibrin matrix into an adjacent external environment”. Support for new claim 14 may be found, for example, in old claims 5 and 7, in the passage found at page 32, lines 2 and 3 and at page 17, line 18 of the description.

Also in new claims 11 and 14, the term “the adjacent external environment” has been replaced with the term “an adjacent external environment”.

Furthermore, in new claims 11 to 18, the phrase “axon growth” was replaced with the phrase “axon sprouting”. Support for this phrase may be found, for example, at page 19, line 31 of the description.

New independent claim 16 was added. This new claim is also based on old claims 1 and 4. More particularly, in new claim 16, the expression “one or two separate component” now refers to “a first matrix forming element” and “a second matrix forming element”. Support for this expression may be found, for example, at page 45, line 25 of the description. The expression “a third container means comprising a therapeutically active

agent selected from the group consisting of C3 and Y-27632 for facilitating axon sprouting at said lesion site” was also added in new claim 16. Support for this expression may be found, for example, at page 32, lines 2 and 3, in the “Examples” section and more particularly at page 36 lines 9-25, and at page 17, line 18 of the description.

New dependent claim 17 was also added. New dependent claim 17 is based on old dependent claim 2 (now new dependent claim 12).

Finally, new dependent claims 13, 15 and 18, where C3 is selected from the group of ADP-ribosyl transferase C3 derived from Clostridium botulinum, a C3 analogue capable of inactivating a Rho GTPase and a recombinant ADP-ribosyl transferase C3, were added. Support for these new dependent claims is summarized below. In addition, methods of making C3 are described, for example, from page 23 to page 27 of the description.

New Claim no.:	Support summary
11	old claims 1 and 4, page 32, lines 2 and 3, page 34, lines 5 to 18, page 45, line 25, page 17, line 18 and page 19, line 31
12	old claim 2, and page 19, line 31
13	page 23, lines 1-5, page 23, lines 15-16, page 19, line 31
14	old claims 5 and 7, page 32, lines 2 and 3, page 17, line 18, and page 19, line 31
15	page 23, lines 1-5 and page 23, lines 15-16, page 19, line 31
16	old claims 1 and 4, page 32, lines 2 and 3, page 36, lines 9-25, page 45, line 25, page 17, line 18, page 19, line 31
17	old claim 2 and page 19, line 31
18	page 23, lines 1-5, page 23, lines 15-16, page 19, line 31

Informalities

Figures

The Examiner has objected to figure 9. The Applicant has amended figure 9 to specify each of the individual elements of this schematic directly in figure 9. More particularly, in figure 9, numerical identifier 4 was given to the additional container means illustrated in dotted outline. The term "additional container means" was also inserted in this pictogram. The term "container means for first matrix forming element" was inserted in pictogram carrying numerical identifier 2. The term "container means for second matrix forming element" was inserted in pictogram carrying numerical identifier 1. The term "mixing container" was inserted in pictogram carrying numerical identifier 6. Finally, the term "container means for therapeutically active agent" was inserted in pictogram carrying numerical identifier 3. Support for each of these expressions may therefore be found at page 45, line 16 to page 46, line 2 and in new claim 11 (see support for new claim 11 below).

The Applicant also hereby takes the opportunity of making editorial modification to page 45 which relates to the description of figure 9. More particularly at lines 17 the "container means for a therapeutically active agent" has now been given numerical identifier 3. Support for this modification may be found, for example, in the expression "feed line 8 is indicative of the addition of C3 (i.e. therapeutically active agent) to container..." at page 45, lines 23 and 24 and from old figure 9 where feed line 8 is clearly linked to container means 3. In addition, at line 24, the Applicant has modified the expression "addition of C3 to the container 8" for the expression "addition of C3 to the container 6". Support for this modification may be found, for example, at page 45, line 22 and in old figure 9 where feed line 8 is clearly linked to container means 6. Finally, the Applicant has inserted numerical identifier 4 to the expression "additional container means" found at line 21.

The Applicant also hereby takes the opportunity of adding new figure 10 as well as a description of new figure 10. Support for new figure 10 and for the description of figure

10 is as described for new figure 9. Additional support may be found, for example, at page 35, lines 9 to 25, at page 45, line 16 to 32 and page 46, lines 1-2.

Sequence Rules

As requested by the Examiner, the Applicant has inserted sequence identifiers at pages 41, 42 and 43 as illustrated in the "Amendment to the specification" section.

The Applicant also hereby takes the opportunity to make amendments to the sequence (SEQ ID NO.:3) found at page 43. More particularly, the second paragraph of page 43 was replaced in order to identify amino acid X found in the following passages; "NIMLFXGDDP" and "LNXHRLEYGY". The identity of amino acids X may be inferred from the corresponding nucleotide sequence found at page 42 starting at line 17 and ending at line 30. Similarly, the passages related to the amino acid content of the recombinant C3 found at page 43 (from line 22 to line 31) and the passage found at page 44 (from line 1 to line 14) were changed to reflect the amended amino acid content.

The replacement paragraph (related to SEQ ID NO.:3) of page 43 finds support on the first paragraph of page 43, whereby the Applicant refers to that particular amino acid sequence as being a "*translation of the above sequence to show amino acid sequence*" and therefore on the nucleotide sequence disclosed at page 42 starting at line 17 and ending at line 30. More particularly the amino acid found in the passage "NIMLFXGDDP" has been identified as R (Arginine) from the nucleotide sequence "TATTTAGAGG" found at page 42 line 23. The amino acid found in the passage "LNXHRLEYGY" has been identified as K (Lysine) from the nucleotide sequence "TTAAATAAG" found at page 42, line 25.

The Applicant also made changes to the Sequence Listing paper copy and computer readable form provided on November 20, 2003 in order to reflect changes made to the specification with respect to the identity of amino acids X as discussed herein.

The Applicant hereby submits a substitute paper copy of the Sequence listing in

compliance with the requirements of 37 CFR 1.822 and/or 1.823 as well as a computer readable form in compliance with the requirements of 37 CFR 1.824.

The Applicant confirms that the substitute paper copy of the Sequence listing does not include new matter. The Applicant also confirms that the sequence listing information recorded in the computer readable form is identical to the substitute paper copy of the Sequence listing and includes no new matter.

Other

The Applicant also hereby takes the opportunity to correct clerical errors in the specification and more particularly to pages 1, 2, 7, 12, 18, 19, 20, 32 and 33 as illustrated in the "Amendment to the specification" section.

In addition, the Applicant has inserted a passage after page 11 which mainly relates to the summary of the invention. Support for this new passage may be found, for example, in old claims 1 to 10 as well as in new claims 11 to 18 (support for new claims 11 to 18 is as described herein).

Claim Rejections/Objections

35 USC § 112, first paragraph-scope of enablement and written description

The Applicant has modified old independent claims 1 and 5, in light of the Examiner's objection. More particularly, old independent claims 1 and 5, has been replaced with new independent claims 11 and 14, which refer to therapeutically acceptable matrix as "a therapeutically acceptable in vivo fibrin matrix" and to therapeutic agent as "a therapeutically active agent selected from the group consisting of C3 and Y-27632".

Thus, new independent claims 11, 14 and 16 as well as dependent claims 12, 13, 15 and 17-18 are now directed to a therapeutically active agent selected from the group consisting of C3 and Y-27632 and a fibrin matrix.

35 USC § 112, second paragraph-indefiniteness

The Applicant has modified old claims 1, 2, 4, 5 and 7 with respect to the phrase “axon growth” and more particularly with respect to the term “growth”. Thus, new claims 11 to 18 now refer to the phrase “axon sprouting”. Support for the expression “axon sprouting” may be found, for example, at page 19, line 31.

35 USC § 102- prior art

The Examiner has objected to old claims 1, 2 and 4 on the ground that the claimed subject matter was anticipated by U.S. Patent 4,631,055 (Redl *et al.*) As mentioned above, old independent claim 1 has been replaced with new independent claim 11. The Applicant respectfully submits that the Redl *et al.* reference does not disclose nor suggest any kit exploiting a first and second matrix forming element capable of forming a therapeutically acceptable in vivo fibrin matrix in combination with C3 or Y27632.

Similarly, with respect to new claim 14, the Applicant respectfully submits that the Redl *et al.* reference does not disclose nor suggest a composition exploiting a combination of C3 or Y27632 with a first matrix forming element capable of forming a flowable carrier component once intermingled with a second matrix forming element, and which elements are further being capable of forming a therapeutically acceptable in vivo fibrin matrix.

Finally, with respect to new claim 16, the Applicant respectfully submits that the Redl *et al.* reference does not disclose nor suggest any three container-kit, comprising a first matrix forming element, a second matrix forming element which elements are being capable of forming a therapeutically acceptable in vivo fibrin matrix and a third container comprising C3 or Y27632.

Therefore, in light of the present amendments, the Applicant respectfully submits that new independent claims 11, 14 and 16 as well as dependent claims 12-13, 15 and 17-

18 are not anticipated nor encompassed by the Redl *et al.* reference and are thus patentably distinct from the cited reference.

The Applicant would also like to bring to the Examiner's attention that a Supplemental Information Disclosure Statement has been submitted on the same date by separate letter.

In view of the Examiner's earlier restriction requirement, the Applicant retains the right to present claims 3, 6, 8, 9 and 10 in a divisional application.

Favorable consideration of the present application in light of the foregoing remarks is respectfully requested. The Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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By

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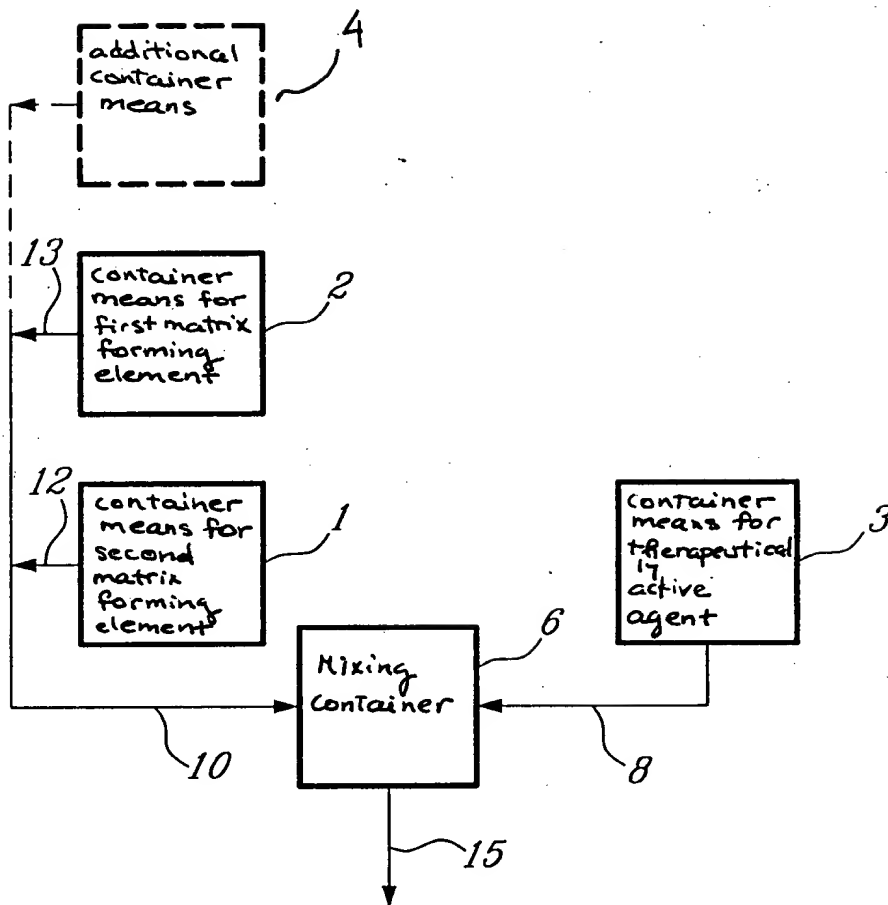


FIG. 9